PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 15 JUL 2005
WIPO PCT

Applicant's or agent's file reference P06297PC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE2004/000452	International filing date *(day/month/year)* 24.03.2004	Priority date *(day/month/year)* 24.03.2003
International Patent Classification (IPC) or both national classification and IPC A61K31/439		
Applicant APREA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.09.2004	14.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Beeck, M Telephone No. +49 89 2399-8473

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SE2004/000452

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-24 as originally filed

Claims, Numbers

1-11 filed with telefax on 20.06.2005

Drawings, Sheets

1/17-17/17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 5

   because:

   ☒ the said international application, or the said claims Nos. 5 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-4,6-11
	No:	Claims	

2. Citations and explanations

see separate sheet

D1: WO 03 070250 A1

SECTION III:

Claim 5 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

SECTION V:

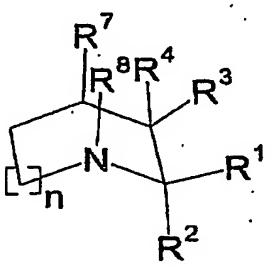
1) The examination has been carried out assuming that the priority is valid, so that P-document D1 has not been taken into consideration.

2) In view of the documents cited in the Search Report the subject-matter of the claims is novel and inventive.

3) For the assessment of the present claim 5 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims (amended) 20.06.2005

1. Use of a compound capable of transferring wild type p53 from an inactive conformation thereof, which conformation is reactive to Pab 240 and not to Pab 1620, into an active conformation capable of inducing apoptosis, which compound is selected from compounds having a structure according to the formula I



(I)

wherein

n is 0,1 or 2;

R^1 and R^2 are the same or different and are selected from –H, $-CH_2-R^5$, $-CH_2-O-R^5$, $-CH_2-S-R^5$, $-CH_2-NH-R^5$, $-CO-O-R^5$, $-CO-NH-R^5$, $-CH_2-NH-CO-R^5$, $-CH_2-O-CO-R^5$, $-CH_2-NH-CO-NHR^5$, $-CH_2-NH-CO-OR^5$, $-CH_2-NH-CS-NHR^5$ and $-CH_2-O-CO-NHR^5$; or R^1 and R^2 are together $=CH_2$;

R^3 and R^4 are the same or different and are selected from –H, -OH, -SH, $-NH_2$, $-NHR^5$ and $-O-CO-C_6H_5$; or R^3 and R^4 together are =O, =S, =NH or $=NR^5$;

R^5 represents the same or different groups selected from H, substituted or non-substituted C1 to C10 alkyl, C2 to C10 alkenyl, C2 to C10 alkynyl, substituted or non-substituted C3 to C12 cycloalkyl, substituted or non-substituted benzyl groups, substituted or non-substituted aryl or mono-, bi-, tricyclic unsubstituted or substituted heteroaromatic ring(s) with one or more heteroatoms and non-aromatic heterocycles wherein

the substituents of the substituted groups are selected from C1 to C10 alkyl, C2 to C10 alkenyl, C2 to C10 alkynyl, halogen, substituted or non-substituted aryl, substituted or non-substituted hetero-aromatic compounds, non-aromatic heterocycles, C1 to C10 alkyloxy, C1 to C10 alkylamino, C2 to C10 alkenylamino, C2 to C10 alkynylamino, COR^6, $CONR^6$ and $COOR^6$;

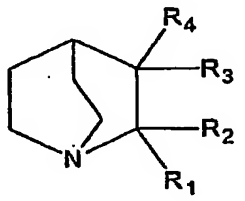
R^6 is selected from H, unsubstituted or substituted C1 to C10 alkyl, C2 to C10 alkenyl or alkynyl, benzyl, aryl, unsubstituted or substituted heteroaromatic rings with one or more hetero-atoms and non-aromatic heterocycles;

R^7 and R^8 together form a bridging CH_2-CH_2 moiety; or R^7 and R^8 are both hydrogen;

or a pharmaceutically acceptable salt or prodrug thereof,

for the preparation of a medicament for use in treating malignant melanoma and/or a pathological condition involving undesired angiogenesis.

2. The use of claim 1, wherein the compound is selected from compounds having the following formula (II)



(II)

wherein:

R_1 and R_2 are independently selected from hydrogen, hydroxymethyl, or a methylene group linked to the nitrogen atom of an amine-substituted phenyl group, to a nitrogen atom contained in the ring structure of a purine, 8-azapurine, or benzimidazol residue, or R_1 and R_2 may together represent a double bonded methylene group, and;

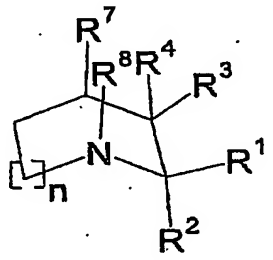
R_3 and R_4 are independently selected from hydrogen, hydroxyl, and benzoyloxy, or R_3 and R_4 may together represent an oxygen atom being double bonded, with the proviso that when either of R_3 and R_4 is a benzoyloxy group, both R_1 and R_2 are hydrogen, or a pharmaceutically acceptable salt or prodrug thereof.

3. The use of claim 2, wherein the compound is selected from 2,2-bis(hydroxymethyl)-1-azabicyclo[2.2.2]octan-3-one, 9-(azabicyclo[2.2.2]octan-3-one)-6-chloro-9H-purine, 2-(hydroxymethyl)quinuclidine-3,3-diol, 2-(adenine-9-methylene)-3-quinuclidinone, 2-methylene-3-quinuclidinone, 2-(-2-amino-3-chloro-5-trifluoromethyl-1-methylaniline)-3-quinuclidinone, 2-(6-trifluoromethyl-4-chlorobenzimidazole-1-methylene)-3-quinuclidinone, 2-(6-methoxypurine-9-

methylene)-3-quinuclidinone, 2-(8-azaadenine-9-methylene)-3-quinuclidinone, 1-azabicyclo [2.2.2]oct-3-yl benzoate, 2-(5,6-dimethyl-benzimidazole-1-methylene)-3-quinuclidinone, 2-(8-azaadenine-7-methylene)-3-quinuclidinone, 2-(7-methylene-1,3-dimethyluric acid)-3-quinuclidinone, or 2-(2,6-dichloro-9-methylenepurine)-3-quinuclidinone, or a pharmaceutically acceptable salt thereof.

4. The use of anyone of the claims 1-3 together with a pharmaceutically acceptable carrier, diluent and/or excipient.

5. A method of treating malignant melanoma and/or inhibiting undesired angiogenesis, comprising administrating to a mammal in need thereof a pharmaceutically efficient amount of a compound selected from compounds having a structure according to the formula I



(I)

wherein

n is 0,1 or 2;

R^1 and R^2 are the same or different and are selected from –H, $-CH_2-R^5$, $-CH_2-O-R^5$, $-CH_2-S-R^5$, $-CH_2-NH-R^5$, $-CO-O-R^5$, $-CO-NH-R^5$, $-CH_2-NH-CO-R^5$, $-CH_2-O-CO-R^5$, $-CH_2-NH-CO-NHR^5$, $-CH_2-NH-CO-OR^5$, $-CH_2-NH-CS-NHR^5$ and $-CH_2-O-CO-NHR^5$; or R^1 and R^2 are together $=CH_2$;

R^3 and R^4 are the same or different and are selected from –H, -OH, -SH, $-NH_2$, $-NHR^5$ and $-O-CO-C_6H_5$; or R^3 and R^4 together are =O, =S, =NH or $=NR^5$;

R^5 represents the same or different groups selected from H, substituted or non-substituted C1 to C10 alkyl, C2 to C10 alkenyl, C2 to C10 alkynyl, substituted or non-substituted C3 to C12 cycloalkyl, substituted or non-substituted benzyl groups, substituted or non-substituted aryl or mono-, bi-, tricyclic unsubstituted or substituted heteroaromatic ring(s) with one or more heteroatoms and non-aromatic heterocycles wherein

the substituents of the substituted groups are selected from C1 to C10 alkyl, C2 to C10 alkenyl, C2 to C10 alkynyl, halogen, substituted or non-substituted aryl, substituted or non-substituted hetero-aromatic compounds, non-aromatic heterocycles, C1 to C10 alkyloxy, C1 to C10 alkylamino, C2 to C10 alkenylamino, C2 to C10 alkynylamino, COR^6, $CONR^6$ and $COOR^6$;

R^6 is selected from H, unsubstituted or substituted C1 to C10 alkyl, C2 to C10 alkenyl or alkynyl, benzyl, aryl, unsubstituted or substituted heteroaromatic rings with one or more hetero-atoms and non-aromatic heterocycles;

R^7 and R^8 together form a bridging CH_2-CH_2 moiety; or R^7 and R^8 are both hydrogen;

or a pharmaceutically acceptable salt or prodrug thereof.

6. Method of testing compounds for the ability of transferring wild type p53 from an inactive conformation into an active conformation comprising the steps:

A. Providing cells carrying only wt and not mutant p53, in which cells inactive wt p53 conformation is present;

B. Exposing the cells *in vitro* to a substance to be tested; and

C. Measuring the cellular inactive wt p53 conformation.

7. The method of claim 6, wherein instead of step C an alternative step C' is used comprising comparing the effect of the tested substance on the cells (carrying functional p53) in step B to the effect on cells or tissues with no or non-functional p53.

8. The method of claim 6 or 7, wherein integrin $\alpha_v\beta_3$ is present in the cells.

9. The method of claim 6-8, wherein the Pab 240 is used for detecting wt p53 in its inactive conformation.

10. The method of any of the claims 6-9, wherein a compound of claim 1 is tested.

11. The method of any of the claims 6-10, wherein the cells in step B are exposed *in vivo* in an animal to the substance to be tested, and the animal subsequently sacrificed.